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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,501	12/31/2001	Etsuro Ogata	04853.0085	1393

22852 7590 05/18/2006

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,501	OGATA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-27* is/are pending in the application.

4a) Of the above claim(s) *12-22* is/are withdrawn from consideration.

5)☒ Claim(s) *26* is/are allowed.

6)☒ Claim(s) *1,4,5,7-11, 23-25 and 27* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 and 4-27 are pending.
It is noted that at page 2 of the remark, applicant stated that claims 1, 4-11, and 23-27 are pending. However, claims 12-22 have never been canceled.

2. Claims 12-22 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. In view of the amendment filed 2/23/06, the following objection and rejections remain.

4. Claim 11 stands objected to for reciting non-elected embodiment.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-5, 7-11, 23-25 and 27 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of ameliorating low vasopressin level comprising administering to a patient a humanized antibody or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, or antibody produced by hybridoma deposited as FERM BP-5631 wherein the antibody or binding fragment thereof inhibits the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor, **does not** reasonably provide enablement for a method of maintaining or increasing low vasopressin level comprising administering to a patient at least one anti-PTHrP antibody, or binding fragment thereof such as any anti-PTHrP antibody, any modified form of any antibody binding fragment, any humanized, or chimeric antibody, any antibody produced by the hybridoma deposited as FERM BP-5631, any monoclonal antibody, that inhibits the binding between PTHrP and a receptor thereof, allowing the antibody to inhibit the binding of PTHrP and its receptor and maintaining or increasing vasopressin level, (2) a method of treating at least any one symptom, any symptom such as polyuria, dehydration, mouth dryness, hyperosmolarity, caused by a decrease in vasopressin level as a results from cancer comprising administering to a

patient at least any one anti-PTHrP antibody, any antibody fragment is bound to a carrier such as PEG, any antibody fragment is Fab, scFv, F(ab')2 or Fv as set forth in claims 1, 4-5, 7-11, and 23-25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO: 75 for a method of inhibiting the binding of parathyroid hormone related protein (PTHrP) to its PTHrP receptor. The specification discloses administering humanized antibody that binds specifically to human PTHrP ameliorates the decreased blood vasopressin levels in mice implanted with human large cell lung carcinoma LC-6, a hypercalcemia model.

The specification does not teach how to make "modified form" of antibody fragment that binds to *all* "PTHrP", much less which particular anti-PTHrP antibody maintains vasopressin level and which particular anti-PTHrP antibody increases vasopressin level in vivo. There is no showing in the specification as filed that administering any anti-PTHrP other than the specific humanized PTHrP antibody that binds to the N terminal 1-34 of human PTHrP or the deposited antibody (Fig 1) resulted in increasing low vasopressin level of any patient. Likewise, there is no showing in the specification as filed that administering any anti-PTHrP other than the antibody that binds to N terminal 1-34 of human PTHrP resulted in *maintaining* vasopressin level in vivo. In fact, the specification shows administering anti-PTHrP up to 3mg/kg has no significant effect on vasopressin levels, note the error bar among the treated and control group overlap (see Figure 3, in particular). The specification discloses that administering humanized PTHrP antibody has

no effect on urine volume (Figure 2). However, at high concentration 3mg/kg, humanized anti-PTHrP treatment ameliorates increased blood osmotic pressure in the hypercalcemia rat.

Further, the specification does not teach any antibody such as monoclonal, humanized, chimeric, antibody fragment and modified form of said fragment that binds to the other part of PTHrP such as C-terminal part of all PTHrP, is effective for inhibiting binding between PTHrP and a receptor thereof, in turn, would be useful as a method of either maintaining or increasing low vasopressin level or a method of treating at least one symptom caused by a decrease in vasopressin level.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody. Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. There is insufficient guidance as to which antigen such as PTHrP would produce antibody that binds to specifically to all PTHrP, in turn, would be useful for a method of maintaining low vasopressin level and which PTHrP antigen would produce antibody that would increase low vasopressin level.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Further, the specification discloses only monoclonal antibody that binds to human PTHrP (1-34) consisting of SEQ ID NO: 75, the binding specificity of other monoclonal antibody, fragment thereof, chimeric and humanized antibody are not enabled.

With regard to modified form of antibody binding fragment, there is insufficient guidance in the specification as filed as to which amino acids within the binding region of the antibody fragment (CDRs) to be modified by amino acid substitution, deletion, addition such that the resulting modified antibody fragment still maintains its binding specificity to human PTHrP.

Since the binding specificity of the antibody in the claimed methods is not enabled, it follows that any monoclonal antibody, chimeric antibody, and humanized antibody and binding fragment thereof that bind to *all* PTHrP for the claimed methods are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/23/06 have been fully considered but are not found persuasive.

Applicants' position is that the specification discloses anti-pTHrp antibody directed to the 1-34 fragment of PTHrP. See specification, Example 1: Preparation of hybridomas producing anti-pTHrp (1-34) mouse monoclonal antibody" pages 23-24. However, the disclosure generally describes how to produce antibodies directed to any portion of PTHrP, using the entire protein as a sensitizing antigen. See specification, pages 5-8. The specification specifically states that "the purified PTHrP protein is used as a sensitizing antigen. Alternatively, a 34-amino acid peptide of the N-terminal region of the PTHrP may be chemically synthesized as the sensitizing antigen." Specification, page 5, lines 26-28. Thus, one of ordinary skill in the art would be able to make and use an antibody directed to any epitope of the PTHrP antigen. Applicants should not be limited to the antibody directed to the N-terminal portion of PTHrP actually reduced to practice. The Office also alleges that one of ordinary skill in the ad would not be able to make or use a "modified form" of a PTHrP antibody. Applicants respectfully disagree. The specification at pages 13-14 states: As a modified form of the above-mentioned antibodies, for example, anti-pTHrp antibody conjugated to any molecule (e.g., polyethylene glycol', PEG) may also be used.

Such modified antibodies are also encompassed in the "antibody" of the present invention. The modified antibodies can be prepared by chemical modifications of the antibodies. The Office also requires identification of which PTHrP antibodies maintain vasopressin level and which increase vasopressin level. Again, this requirement is not part of the enablement test outlined above. The disclosure contains sufficient information by which one of ordinary skill in the ad can test to determine if a particular PTHrP antibody maintains or increases vasopressin level. Even if inoperative embodiments exist, the binding and neutralizing activity of the antibody can be easily tested to select the antibodies that maintain or increase vasopressin levels. See specification at page 16. Furthermore, the specification teaches the use of a tumor-transplanted animal model to determine if a particular antibody maintains or increases vasopressin level in vivo. See specification at pages 19-23. No undue experimentation is required by one of ordinary skill in the art to select an antibody that maintains or increases Vasopressin levels.

In response, enablement is not commensurate in scope with the method of maintaining or increasing low vasopressin level in which any one or more antibodies to any PTHrP is administered to a patient. The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO: 75 for a method of ameliorate low vasopressin level resulted from cancer. The specification discloses administering only humanized antibody that binds specifically to human PTHrP ameliorate the decreased blood vasopressin levels in mice implanted with human large cell lung carcinoma LC-6, a hypercalcemia model. Other than the human PTHrP and the N-terminal 1-34 of human PTHrP as the antigen for making antibody that inhibits the binding between human PTHrP and its receptor, the specification does not teach any other PTHrP and whether antibody made using human PTHrP binds to PTHrP from other species, in turn, inhibit the binding between PTHrP from other species and its receptor for the claimed method of maintaining or increasing low vasopressin level in a patient. Further, there is insufficient guidance as to the binding specificity of any anti-PTHrP antibody made by immunizing either the full-length (claim 27) or C-terminal half of human PTHrP or any PTHrP. Given the numerous anti-PTHrP antibody, it is unpredictable which anti-PTHrP is effective for maintaining or increasing low vasopressin level. As evident by the teachings of Kuby *et al*, of record, that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular).

Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. As such, it would require undue experimentation to practice the claimed invention. It is noted that claim 27 was inadvertently left out in the previous Office Action. However, reading the content of the rejection and applicant's response to the rejection is clear that claim 27 is supposed to be included in this rejection. The Examiner apologizes for the inadvertent error.

With respect to the argument that the specification discloses chemically modified antibodies, for example, anti-pTHrp antibody conjugated to any molecule (e.g., polyethylene glycol', PEG), enablement is not commensurate in scope with the method of maintaining or increasing low vasopressin level in which any one or more modified antibody binding fragment to any PTHrP is administered to a patient. Claim 4 does not recite the method wherein the antibody binding fragment is conjugated to polyethylene glycol. The "modified form" of antibody fragment to any PTHrP encompasses any modification such as amino acid substitution, deletion, addition, and combination thereof within CDRs of the antibody fragment. There is insufficient guidance in the specification as filed as to which amino acids within the binding region of the antibody fragment (CDRs) to be modified by amino acid substitution, deletion, addition such that the resulting modified antibody fragment still maintains its binding specificity to human PTHrP, in turn, would be useful for maintaining or increasing low vasopressin level in a patient. Accordingly, the modified form of antibody fragment in claim 4 is not enabled.

7. Claims 1, 4-5, 7-11, and 23-25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for any antibody such as any monoclonal, humanized, chimeric, antibody fragment and any "modified form" of said fragment that binds to *all* "PTHrP" and *any* part of PTHrP other than N-terminal 1-34 of human PTHrP for a method of *maintaining* or *increasing* low vasopressin level.

The specification discloses only a method of making antibody such as human, chimeric, humanized antibody and binding fragment thereof that binds specifically to the N terminal 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO: 75 for a method of

ameliorate low vasopressin level resulted from cancer. The specification discloses administering only humanized antibody that binds specifically to human PTHrP ameliorate the decreased blood vasopressin levels in mice implanted with human large cell lung carcinoma LC-6, a hypercalcemia model.

With the exception of the specific antibody mentioned above that binds specifically to the N-terminal of human PTHrP1-34 consisting of the amino acid sequence of SEQ ID NO: 75, and the hybridoma deposited as FERM BP-5631, there is insufficient written description about the binding specificity of all other antibody such as monoclonal, humanized, chimeric, and binding fragment thereof such as modified binding fragment thereof that bind to other PTHrP for the claimed method. There is inadequate written description about the structure of the CDRs of all antibodies that correlate with functions such as which antibody maintains vasopressin levels while which antibody increases vasopressin levels upon administering to a patient. Further, there is insufficient written description about which amino acids within the binding fragment of any antibody to be modified by substitution, deletion, addition and/or combination thereof such that the "modified binding fragment" still maintains its binding specificity to human PTHrP of SEQ ID NO: 75.

Other than N-terminal of human PTHrP1-34 to which the antibody binds for the method of ameliorating low vasopressin level in a patient, the binding specificity of the antibody to other part of PTHrP1-34 other than terminal of human PTHrP1-34 in the claimed method is not adequately described. Given the lack of any additional parathyroid hormone related peptide (PTHrP) and C-terminal part of PTHrP to which the antibody binds, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of PTHrP to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/23/06 have been fully considered but are not found persuasive.

Applicants' position is that contrary to the Office's assertion, the written description requirement does not necessitate "written description about the structure of the CDRs of all antibodies that correlate with function." Furthermore, the claims should not fail the written

description requirement because "there is insufficient written description about which amino acids within the binding fragment of any antibody to be modified by substitution, deletion, addition and/or combination thereof such that the 'modified binding fragment' still maintains its binding specificity." Finally, the structure of full-length PTHrP is disclosed in the specification at, for instance, page 5, lines 19-21, in the Suva et al. reference. Based on the Office's own guidelines and the holdings of the courts, Applicants assed that the claims fulfill the written description requirement and request that the Office withdraw this rejection.

In response to the argument that the structure of full-length PTHrP is disclosed at page 5 of the specification, the specification at page 5 discloses only human PTHrP, not PTHrP from any species. The specification does not describe the binding specificity of any and all antibodies that bind to the full-length PTHrP from any species, including human PTHrP. The specification does not describe the binding specificity of any and all antibodies that bind to the C-terminal half of any PTHrP, in turn, the antibody could inhibit the binding of any PTHrP to its receptor for the claimed method of maintaining or increasing low vasopressin level in all patient.

With regard to modified form of antibody binding fragment in claim 4, the "modified form" of antibody fragment to any PTHrP encompasses any modification such as amino acid substitution, deletion, addition, and combination thereof within CDRs of the antibody fragment. There is a lack of a written description about amino acids within the binding region of the antibody fragment (CDRs) to be modified by amino acid substitution, deletion, addition and combination thereof such that the resulting modified antibody fragment still maintains its binding specificity to human PTHrP, in turn, would be useful for maintaining or increasing low vasopressin level in a patient. The rejection of claim 4 would be obviate by amending the claim 4 to recite the method according to claim 4 wherein the antibody is an antibody binding fragment thereof or wherein the antibody binding fragment is conjugated to polyethylene glycol (PEG).

8. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Claim 26 is allowed.

10. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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